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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/702,525	02/07/97	SHARPE	A BWI-120CPUS

EXAMINER
GAMBEL, P.

ART UNIT	PAPER NUMBER
1642	11

DATE MAILED: 03/17/98

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LAHIVE & COCKFIELD, LLP
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 12/22/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-77 is/are pending in the application.
Of the above, claim(s) 18-29, 32, 48-59, 62, 66-68, 73-74 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-17, 30-31, 33-47, 60-61, 63-65, 69-71, 75-77 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892 → SEE ACTION
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

Detailed Action

1. Effective 2/7/98, the location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1642, Technology Center 1600.

2. Applicant's amendment, filed 12/22/97 (Paper No. 10), is acknowledged.
Claims 1, 33, 42, have been amended.
Claim 77 has been added.

Applicant's election with traverse of Group I in Paper No. 10, filed 12/22/97, is acknowledged. Upon reconsideration of applicant's arguments and in the interest of compact prosecution, claims 1-17, 30-31, 33-47, 60-61, 63-65, 69-71 and 75-77, drawn isolated nucleic acids which binds CD28 or CTLA-4 as newly formed Group I is under consideration.

Claims 18-29, 32, 48-59, 62, 66-68, 73-74 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention. In view of applicant's election of newly formed Group I, applicant's election is considered an election without traverse.

3. Applicant's IDS, filed 7/14/97 (Paper No. 7) is acknowledged, however the 1449 could not be located in the application. Therefore, the reference provides are cited on a PTOL 892.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed, including nucleic acids encoding proteins that bind CD28 or CTLA-4.

5. The drawings submitted with this application were declared informal by the applicant. Accordingly, they have not been reviewed by draftsperson at this time. When formal drawings are submitted, the draftsperson will perform a review.
Direct any inquiries concerning drawing review to the Drawing Review Branch (703) 305-8404.

6. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

7. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-8, 33-39 and 77 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed: the recitation of "is not any of the following" in claims 1, 33 and 77.

Applicant's amendment, filed 12/22/97 (Paper No. 10) indicates support can be found in claims as originally filed as well as throughout the specification. While the specification and original claims provide written description for the recited negative limitations as they read on the members of the Markush claims, applicant has not provided sufficient guidance and direction for the negative limitation to read "any of the following nucleotide sequences", that is, the combination of all of the members of the Markush claims. For example, adding the expressed exclusion of certain elements implies the permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations do, in fact, introduce new concepts. See Ex parte Grasselli, 231 USPQ 393 (BPAI). The specification as filed does not provide a written description or set forth the metes and bounds of the negative limitation. The specification does not provide sufficient blazemarks nor direction for the above-mentioned "limitations" as they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action

9. Claims 1-15, 17, 30-31, 33-45, 60-61, 63, 69, 75-77 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are indefinite in that they only describe the "isolated nucleic acids encoding a protein which binds CD28 or CTLA-4" by reciting various elements (e.g. first exon, second exon, third exon, fourth exon, fifth exon), a proviso that certain elements are not any of the following nucleotide sequences set forth in a Markush, or the nucleotide sequence is derived from costimulatory molecule gene. While these characteristics may have some notion of the specificity of the nucleic acids, these claims lack sufficient structural information or defining characteristics which distinctly claims the isolated nucleic acids, including the various elements (e.g. exons, domains). Claiming biochemical molecules by generic terms such as exons, domains, immunoglobulin variable region-like or by particular name given to the encoded protein (i.e. B7-1, B7-2) fails to distinctly claim what that isolated nucleic acid is and what it is made up of. Also, it is noted that it is not clear what the various exons or domains should be (e.g. second cytoplasmic domain in claim 9).

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the ill-defined number of nucleic acids broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, the instant specification discloses a limited number of alternative spliced forms of costimulatory molecules. In addition, applicant has not provided sufficient biochemical information (e.g. sequence) that distinctly identifies the intended elements (e.g. domains, exons) of the claimed nucleic acids. Also, the claims recites negative limitations with respect to other known nucleic acids encoding B7-1 or B7-2, however there is insufficient guidance and written description for the breadth of the claimed nucleic acids. Predicting structural determinations to ascertain functional aspects of the nucleic acids to encode functional protein which bind CD28 and CTLA-4 and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

Further, the claims are not even limited to clearly defined number of nucleic acids encoding CD28-/CTLA-4-binding proteins, but further extend to an ill-defined number of species which share one or more functional or structural characteristics with the B7-1 or B7-2 molecules attributed to in the specification. As the specification does not teach how to make or use a number of species that would be commensurate in scope with the claims, it is found that it would require undue experimentation practice the invention in a manner commensurate in scope with the claims.

It was found in Amgen v. Chugai, 18 USPQ 2d 1017 at 1021, that: "A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. See Oka, 849 F. 2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method or preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having nor more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated."

This position was further supported in Fiers v. Sugano, where it was stated: "An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself" (26 USPQ2d 1601 at 1606). Thus, the instant specification does not adequately describe, and therefore *cannot* adequately teach how to make, the claimed invention.

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the isolated nucleic acids in manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions, insertions or substitutions of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made in the nucleic acids encoding a protein's structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

Applicant has not enabled targeting CD28-specific inhibitory ligands that with specificities other than CD28-specific antibodies that are specific for the same specificity as mAb 9.3 or than soluble CTLA-4. The specification does not appear to specifically define the metes and bounds of "inhibitory ligands other than the specificities indicated in the previous sentence. It is not sufficient to define a specificity by an ill-defined functional property or ambiguous structural properties such as natural, synthetic or recombinant. Stimulating the extracellular domain of the CD28 receptor is ambiguous without defining the endpoints of such stimulation Also, one does not stimulate a domain of a protein as much as one stimulates a function of a system. The instant methods are ill-defined, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property (e.g. structural or functional). Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use of the claimed inhibitory ligands in manner reasonably correlated with the scope of the claims broadly including any number of possible inhibitory ligands. For example, since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. Minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. Therefore, structurally unrelated compounds encompassed by the claimed CD28 inhibitory ligands would be expected to have greater differences in their activities. However, applicant has not provided limited biochemical information for the particular inhibitory ligands 9.3 antibody and soluble CTLA-4 . Therefore, the problem of predicting protein structure from such limited information of a single protein and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the inhibitory protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation. Insufficient direction or guidance is provided to assist one skilled in the art in the selection of any other inhibitory ligands nor is there evidence provided that other such ligands can bind CD28 but not stimulate CD28-mediated interactions. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, making and using CD28 ligand inhibitors would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

12. Claims 1-7, 9-16, 30-31, 33-35, 40-41, 63-65, 69-71 and 75-77 are rejected under 35 U.S.C. § 102(b) as being anticipated by Freeman et al. (J. Exp. Med. 174:625-631, 1991). Freeman teaches nucleic acids encoding murine and human B7-1.

It is noted that applicant may be interpreting the claims to read on negative limitations readings on the combination of all members of Markush claims, however the Markush language provides for the negative limitations reading on individual members of the Markush. Therefore, the claims are met by the prior art.

13. Claims 1-4, 6-7, 9-12, 14-16, 30-31, 33-35, 40-41, 63-65, 69-71 and 75-77 are rejected under 35 U.S.C. § 102(b) as being anticipated by Selvakumar et al. (Immunogenetics 36:175-181, 1992). Selvakumar et al teaches nucleic acids encoding human B7-1.

It is noted that applicant may be interpreting the claims to read on negative limitations readings on the combination of all members of Markush claims, however the Markush language provides for the negative limitations reading on individual members of the Markush. Therefore, the claims are met by the prior art.

14. Claims 1-5, 7, 9-13, 15-16, 30-31, 33-35, 40-41, 63-65, 69-71 and 75-77 are rejected under 35 U.S.C. § 102(a) as being anticipated by Selvakumar et al. (Immunogenetics 38:292-295, 1993). Selvakumar et al teaches nucleic acids encoding murine B7-1.

It is noted that applicant may be interpreting the claims to read on negative limitations readings on the combination of all members of Markush claims, however the Markush language provides for the negative limitations reading on individual members of the Markush. Therefore, the claims are met by the prior art

15. Claims 1-4, 6-7, 9-12, 14-16, 30-31, 33-35, 40-41, 63-65, 69-71 and 75-77 are rejected under 35 U.S.C. § 102(b) as being anticipated by Freeman et al. (J. Immunol. 143:2714-2722, 1989). Freeman teaches nucleic acids encoding human B7-1.

It is noted that applicant may be interpreting the claims to read on negative limitations readings on the combination of all members of Markush claims, however the Markush language provides for the negative limitations reading on individual members of the Markush. Therefore, the claims are met by the prior art

16. Claims 1-3, 33-37, 39-44, 46-47, 60-61, 63, 69 and 75-77 are rejected under 35 U.S.C. § 102(a) as being anticipated by Freeman et al. (J. Exp. Med. 178:2185-2192, 1993). Freeman et al. teaches nucleic acids encoding murine B7-2.

It is noted that applicant may be interpreting the claims to read on negative limitations readings on the combination of all members of Markush claims, however the Markush language provides for the negative limitations reading on individual members of the Markush. Therefore, the claims are met by the prior art

17. Claims 1-3, 33-36, 38-43, 45-46, 60-61, 63, 69 and 75-77 are rejected under 35 U.S.C. § 102(a) as being anticipated by Freeman et al. (Science. 262:909-911, 1993). Freeman et al. teaches nucleic acids encoding human B7-2.

It is noted that applicant may be interpreting the claims to read on negative limitations readings on the combination of all members of Markush claims, however the Markush language provides for the negative limitations reading on individual members of the Markush. Therefore, the claims are met by the prior art

18. Claims 1-3, 33-36, 38-43, 45-46, 60-61, 63, 69 and 75-77 are rejected under 35 U.S.C. § 102(a) as being anticipated by Azuma et al. (Nature 366:76-77, 1993). Azuma et al. teaches nucleic acids encoding human B7-2.

It is noted that applicant may be interpreting the claims to read on negative limitations readings on the combination of all members of Markush claims, however the Markush language provides for the negative limitations reading on individual members of the Markush. Therefore, the claims are met by the prior art

19. Claims 1-6, 9-16, 30-31, 33-41, 43-47, 60-61, 63-65, 69-71 and 75-77 are rejected under 35 U.S.C. § 103 as being unpatentable over any of
Freeman et al. (J. Exp. Med. 174:625-631, 1991)
Selvakumar et al. (Immunogenetics 36:175-181, 1992).
Selvakumar et al. (Immunogenetics 38:292-295, 1993)
Freeman et al.(J. Immunol. 143:2714-2722, 1989)
Freeman et al. (J. Exp. Med. 178:2185-2192, 1993).
Freeman et al. (Science. 262:909-911, 1993) or
Azuma et al. (Nature 366:76-77, 1993).
as the claims read appropriately on nucleic acids encoding B7-1 or B7-2 variants or nucleic acids, vectors and host cells that comprise a signal peptide domain for their expression. The prior art differs from the claimed invention by not all of the allelic variants and signal sequences encompassed by the claims.

Any of the above references teach nucleic acid sequences which encode B7 costimulatory molecules, which can be expressed. However, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use a various signal sequences for expression of the protein for various uses, including large volumes and bacterial cell expression. In addition, the ordinary artisan would have expected and would have expected to obtain minor modifications (substitutions, additions, deletions or insertions) for example due to allelic variation. A person of ordinary skill in the art would have been motivated to do so for secretion of the protein from the bacterial cell. Therefore it an isolated protein expressed by a construct not having the above listed signal sequences would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made in view of the above cited references and the contemporary knowledge in the art at the time the invention was made.

20. No claim is allowed.

SEQ ID NOS. 4 and 5 are free of the prior art.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[lila.feisee@uspto.gov]**.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Phillip Gambel, Ph.D.
Patent Examiner
Technology Center 1600
March 15, 1998

SEE NEXT PAGE

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16. If applicant desires priority under 35 U.S.C. § 120 based upon a parent application, specific reference to the parent application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. Status of the parent application (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "Patent No." should follow the filing date of the parent application. If a parent application has become abandoned, the expression "abandoned" should follow the filing date of the parent application.

Applicant should provide the current status of the parent application on the first line of the specification.